IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Attorney Docket No. 006420.00003)

In the Application of:	)	
	)	
Arora, et al.	)	
	)	Examiner: Clark, Amy L.
Serial No.: 10/525,992	)	
	)	Group Art Unit: 1655
Filing Date: February 28, 2005	)	
	)	
For: Herbal Extract Comprising A Mixture of Saponins Obtained From Sapindus Trifoliatus for Anticonvulsant Activity	)	

DECLARATION OF SUDERSHAN K. ARORA UNDER 37 C.F.R. 1.132

1. I, Sudershan K. Arora, declare as follows.

2. I am an inventor named in the present application. My present title is President – Novel Drug Discovery & Development of Lupin Ltd. My curriculum vitae is attached as Exhibit 1 hereto.

3. I am submitting this Declaration in response to the Office Action mailed August 9, 2006 in the subject patent application.

4. Table 1 below is a redacted excerpt from the specification of the present patent application (page 19).

Table 1: Disclosure in US 10/525,992

S.No.	Receptor	Percent inhibition with *Sapindus trifoliatus*	
		2.5 µg/ml	**250 µg/ml**
1	GABA A, agonist Site	50.92	102.40
2	Glutamate AMPA Site	5.43	87.36
3	Glutamate Kainate Site	-15.70	87.29
4	Glutamate NMDA agonist Site	7.27	98.14
5	Glutamate NMDA glycine (Strychnine insensitive) site	14.50	85.33
6	GABA chloride TBOB	-5.12	85.03
7	Glutamate chloride	-2.72	89.49
8	Sodium site-2	19.98	69.54

5. A criterion of 50% inhibition or greater may be used to qualify a compound as active in binding experiments. *See* Exhibit 5 to this Declaration (literature specification from Novascreen).

6. As shown in Table 1, at 250 µ/ml, *Sapindus trifoliatus* is qualified as active under the Novascreen criterion.

7. *Emblica officinalis* was tested for binding towards the sites listed in the above table. Receptor binding assays were conducted at Novascreen, U.S.A. The results are summarized in Table 2 hereinbelow (See Exhibit 4).

Table 2: Receptor Binding affinity with the extract of *Emblica officinalis*

S.No.	Receptor	Percent Inhibition with *Emblica officinalis*	
		2.5 µg/ml	**250 µg/ml**
1	**GABA A agonist Site**	**64.09**	**102.22**
2	**Glutamate AMPA Site**	-10.07	**56.20**
3	Glutamate Kainate Site	-1.12	39.30
4	**Glutamate NMDA agonist Site**	14.90	**71.82**
5	Glutamate, NMDA glycine (Strychnine insensitive) site	0.48	28.21
6	GABA chloride TBOB	-1.95	-0.03
7	Glutamate chloride	28.28	49.24
8	Sodium site-2	7.11	3.93

8. As seen, *Emblica officinalis* at 250 µg/ml fails the Novascreen criterion for Glutamate Kainate site, Glutamate, NMDA glycine (Strychnine insensitive) site, GABA chloride, TBOB, Glutamate chloride, and Sodium site-2.

9. An antimigraine formation prepared as per Gupta et al. was also tested for binding towards the foregoing sites (see Exhibit 4). The results are summarized in Table 3.

Table 3: Receptor Binding affinity with the antimigraine formulation mentioned in Gupta et al patent.

S.No.	Receptor	Percent inhibition (Gupta et al composition)	
		2.5 µg/ml	**250 µg/ml**
1	GABA A, Agonist Site	19.21	**95.95**
2	Glutamate, AMPA Site	-0.89	41.69
3	Glutamate, kainate Site	-1.16	25.68
4	Glutamate, NMDA agonist Site	15.26	**66.02**
5	Glutamate, NMDA glycine (Strychnine insensitive) site	4.03	42.60
6	GABA chloride,TBOB	-14.60	-3.77
7	Glutamate chloride	1.95	**84.35**
8	Sodium site 2	13.37	3.30

10. Gupta et al. showed markedly reduced binding relative to the inactive composition. Gupta et al. satisfied the 50% inhibition criterion only for three sub-types of receptors, and failed to satisfy the 50% inhibition criterion for Glutamate AMPA site, Glutamate Kainate site, Glutamate NMDA glycine (Strychnine insensitive) site, GABA chloride, TBOB, and Sodium site 2.

11. The saponin content of *Sapindus trifoliatus* and *Emblica officinalis* were evaluated via high performance liquid chromatography, conducted according to the following protocol:

Quantitative Analysis of Raw Material by High Performance Liquid Chromatography (HPLC)

Preparation of the sample: About 1g of the fruit pericarp powder was accurately weighed into a 250ml round bottom flask (RB Flask). 100ml water was added to the same and the total weight of the flask was noted. The content of the flask was then refluxed for 2hrs at 100°C. After cooling the flask was weighed again and water was added to adjust the lost volume to make up the solution to 250ml. From this sample solution, 20ml was transferred to a 100ml RB Flask and 5ml of 50% methanolic-HCl was added to it. The solution was then refluxed at 100 ^{0}C for 2hrs and then evaporated to dryness. The residue was dissolved in 10ml of diluent (A mixture of THF and Methanol in the ratio 30:70 v/v) and carefully transferred to 50ml volume. The samples were analysed and the saponin content were estimated as hederagenin by a quantitative HPLC method similar to that described hereinafter.

12. The following results were observed:

1. Total saponin content of *Sapindus trifoliatus* pericarp was analyzed as hederagenin and was found to be 2.65% w/w.

2. In case of *Emblica officinalis* fruit, hederagenin content was below the detection limit.

3. In the mixture of *Sapindus trifoliatus* and *Emblica officinalis* (1:1) hederagenin content was 1.01% w/w.

13. These results demonstrate that any hederagenin in the mixture of Gupta originated from the extract of *Sapindus trifoliatus* pericarp and that the presence of extract of *Emblica officinalis* deters the amount of hederagenin reducing the total content which is surprising.

14. For further verification, thin layer chromatographic analysis was performed. The analysis was performed according to the following protocol.

Thin Layer Chromatography (TLC) Materials and methods

A. Sample Preparation for the finger printing by TLC of 1% nasal spray: 1.5 mL of the sample was taken in a 10 mL volumetric flask and the volume was made up to mark with water. The content was carefully transferred to a 50 mL-separating funnel and extracted with 5 mL of n-Butanol 3 times. The organic layer was collected. The combined extract was transferred to a 50 mL round bottom flask and evaporated to dryness. The residue thus obtained was dissolved in about 2 mL methanol

B. Sample Preparation for Raw material: Around 1.0 gm of sample was taken in a 250 mL round bottom flask. 100 mL of water was added and refluxed at 100 ^{0}C for 2 hours. 10mL of extract was carefully transferred to a 50mL-separating funnel and extracted with 5 mL of n-Butanol 3 times. The organic layer was collected. The combined extract was

transferred to a 50mL round bottom flask and evaporated to dryness. The residue thus obtained was dissolved in about 2mL methanol.

C. Mobile Phase: Ethyl Acetate : Methanol : Water (80:10:10)

D. Detection: TLC plate is sprayed with 10% acqueous sulfuric acid, charred by heating and observed visually.

Details Of samples spotted on The TLC plate:

Raw Material:

Spot No	Details	Sample ID
1	*Sapindus trifoliatus*	SKJ-20-181-1
7	(1:1) Mix of *Sapindus trifoliatus* and *Emblica officinalis*	SKJ-20-181-5
13	Emblica officinalis	SKJ-20-181-3

Compositions:

Spot No	Details	Sample ID
2	Composition of the present invention (1% w/v)	SKJ-20-181-2
12	Composition of Gupta et al (1% w/v)	SKJ-20-187-6
18	Composition comprising (1%w/v) of *Emblica officinalis*	SKJ-20-187-4

15. The Figure attached as Exhibit 2 shows the qualitative TLC chromatogram. Spots 1, 7, and 13 are of extracts of the raw materials, namely *Sapindus trifoliatus*, and a 1:1 mixture of these two, respectively. The bands corresponding to sapinons are marked in the figure. *Emblica officinalis* does not show any band corresponding to the saponins, whereas *Sapindus trifoliatus* does show a band corresponding to saponins. The Figure is not intended to be a qualitative TLC chromatogram, and the intensities of the bands are not deemed to have relevance.

16. *In vivo* toxicology studies were performed in rats and dogs:

A. Rats: Antimigraine Formulation (3%) according to Gupta et al. patent, *Sapindus trifoliatus* (3%) and Mixture of *Sapindus trifoliatus* and *Emblica officinalis* (3%; 60:40) were studied for nasal irritancy. None of the formulations were found to be irritant to nasal mucosa, turbinate, bronchi and lungs.

B. Dogs: Antimigraine Formulation (1%) according to Gupta et al. patent, *Sapindus trifoliatus* (1%) and Mixture of *Sapindus trifoliatus* and *Emblica officinalis* (1%) were

studied for nasal irritancy. None of the formulations were found to be irritant to nasal mucosa, turbinate, bronchi and lungs.

17. Applicants have assayed saponins as hederagenin in the compositions as compared with the compositions of Gupta et al. The details are provided hereinbelow:

HPLC Assay of Saponins As Hederagenin In Anti-Migraine Nasal Preparation
Reagents used
Formic Acid (AR Grade)
Acetonitrile (HPLC Grade)
Water (Milli Q Grade)
Methanol (HPLC Grade)
Tetrahydrofuran (HPLC Grade)
Hydrochloric acid (AR Grade)

Preparation of Diluent
A mixture of THF and Methanol in the ratio 30:70 v/v was used as a diluent

Preparation of Standard Solution: About 50 mg of Hederagenin working standard was weighed and transferred to a 50 mL volumetric flask. 20 mL of diluent was added and sonicated to obtain a clear solution. The volume was made up using the diluent. 5mL of the standard solution was pipetted into a 50 mL volumetric flask and the volume was made up with methanol. The resulting solution was filtered through a 0.45 μ membrane filter. Estimation of Saponins as Hederagenin content in 1% Nasal Preparation of Gupta et. al. and present invention by acid hydrolysis. 15 mL of the samples were taken separately in a 100mL round bottom flask. 5ml of 50% methanolic hydrochloric acid was added and refluxed at 100 ^{0}C for 2 hours. The solutions were cooled and evaporated to dryness. 10 mL of diluent was added to each residue and sonicated for about 2 minutes. The contents were carefully transferred to 50 mL volumetric flasks and the volume was made up with methanol. The solutions were filtered through a 0.45 μm membrane filters. The above samples were analyzed in HPLC. The chromatographic conditions are as given below:

Instrumentation: A high performance liquid chromatograph system with gradient elution capability, autosampler with cooling chamber (Shimadzu class VP series) or equivalent.

Data handling system (Class VP, version 5.032 or equivalent): Analytical column: A stainless steel column 250 cm long, 4.6 mm in diameter filled with Octadecyl silica gel particle of 5 μm in diameter.(Used Kromasil C-18, 5μm (250 mm x 4.6 mm)

Preparation of Buffer: 1.0 mL of formic acid was added to 1000 mL volumetric flask and made up to the volume with water. The solution was filtered through a 0.45 or finer porosity membrane filter and degassed.

Chromatographic Parameters

Mobile Phase	:	25:75 (Buffer : Acetonitrile)
Flow rate	:	1 mL/min
Detector	:	UV at 205nm
Injection Volume	:	50 µL
Run time	:	20 min

Procedure: 50 µL of standard in triplicate and the specified sample solution in duplicate was injected, into the chromatograph. The chromatograms were recorded and the peak area of the main peak from the chromatographic report was measured. The retention time for Hederagenin was about ~ 7.75min.

Calculations

$$\text{Total saponins as Hederagenin (mg/mL)} = \frac{AT}{AS} \times \frac{DS}{DT} \times \frac{P}{100}$$

Where

AT = Average area counts of Hederagenin peak in the chromatogram of the sample solution

AS = Average area counts of Hederagenin peak in the chromatogram of the standard solution

DS = Dilution factor of the standard solution in mg/mL

DT = Dilution factor of the sample solution in mL/mL

P = Percent potency of Hederagenin working standard, on as is basis.

Details of Samples:

S. No.	Batch No	No of injections	Decoding	Figure Number
1	SKJ-22-183	3	Hederagenin Working STD (LLL3344)	Figure 1, 2, 3
2	NP-50-197	2	Formulation by Gupta et al Method	Figure 4, 5
3	LLL3344 Hederagenin	3	Hederagenin Working STD (SKJ-22-183)	Figure 6, 7, 8
4	MB-50-193	2	Formulation by Present invention Method	Figure 9, 10

18. The results obtained are tabulated in the following tables as given below (see also Exhibit 3).

TABLE A: Assay of 1% Anti-Migraine Nasal Preparation, Prepared By Gupta et al

SAMPLE NAME	Quantity taken	Makeup volume (mL)	Concentration	Area	Average area	Assay (mg /mL)

STD **STD POTENCY** **96.88** % w/w on as is basis	51.2 mg	500	**0.1024** (mg/mL)	2844979 2839659 2821331	**2835323** RSD 0.44%	
NP-50-197 (1% Formulation)	15 mL	50	**0.3** (mL/mL)	1219681 1220741	**1220211** RSD 0.06%	0.1423

TABLE B: Assay of 1% Anti-Migraine Nasal Preparation, Prepared By Present invention

SAMPLE NAME	Qtantity taken	Makeup volume (mL)	Conc.	Area	Average area	Assay (mg /mL)
STD **STD POTENCY** **96.88** % w/w on as is basis	47.1 mg	500	**0.0942**	**2697556** **2695518** **2693713**	**2695596** **RSD** **0.07%**	
MB-50-193 (1% Formulation)	15 mL	50	0.3	2868579 2878626	2873603 **RSD** **0.25%**	0.3243

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 of the laws of the United States, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FURTHER DECLARANT SAYETH NOT

Sudershan K. Arora

Executed on: Feb. 9, 2007
Date

Dr. Sudershan K. Arora
President
Novel Drug Discovery & Development
Lupin Research Park, (Lupin Limited)
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EXHIBIT 1

Sudershan K. Arora, Ph.D.

2005- Present	President – Novel Drug Discovery & Development Lupin Research Park (Lupin Limited) Pune
2004-2005	Global Head R&D Sandoz GmbG (A Novartis Company) Biochemiestr, 10 6250 Kundl Austria
2000 – 2004	President – New Chemical Entity Research Lupin Research Park (Lupin Limited) Pune
1997 – 00	Vice President, New Drug Discovery Research Ranbaxy Laboratories Ltd Gurgaon
1993 – 97	Sr. Manager – R&D Biogen Inc, Cambridge, MA, USA
1987 – 93	Sr. Director – Drug Discovery & Process Research Greenwich Pharmaceutical, Fort Washington, PA, USA
1982 – 87	Post-Doc University of Illinois at Chicago, USA (Dr. J. Kagan & Dr. D.L. Venton)
1979 – 82	Manager – Process Research & New Molecules Union Carbide, Bhopal
1978 – 79	Lecturer, S.D. College, Pathankot
1977	Ph.D. Kurukshetra University (Medicinal Chemistry)

Areas of Expertise:

Drug Discovery and Development, Process Chemistry (API & new molecules) and Phytochemistry.

Major Accomplishments

- Established state-of-art Lupin R&D Centre in Pune.
- Filed 9 IND Applications (3 – USA & 6 – India)
- BPH Compound is in Phase – II clinical trials
- VLA_4 (Asthma) compound is in Phase – II clinical trials
- Amigra – Anti-migraine compound Clinical Phase II completed

- ❖ Desoris – Anti-psoriasis compound Clinical Phase II completed
- ❖ Desoside-P-Anti-psoriasis compound is in Phase-I clinical trial
- ❖ LL-3858-Sudoterb – Anti-TB compound is in Phase-I clinical trial
- ❖ Process Development of various Generic Products/New molecules in India & USA
- ❖ 37 Publications in Peer reviewed journals
- ❖ 25 US patents
- ❖ 10 India Patents
- ❖ DST-CSIR-Lupin Collaboration(IICT-HYD,NCL-PUNE, IISC-BANGALORE)
- ❖ Active Participant in NMITLI (CSIR) projects (CDRI-LUCK, NCL-PUNE, IICT-HYD)

Awards

- ❖ Honorary Professor for Life, Department of Life Sciences, Bundelkhand University, Jhansi, U.P. (February, 2001)
- ❖ Professor A.S.R. Anjaneyulu Award, awarded by Indian Chemical Society, Kolkata (December, 2002)
- ❖ S.S. Katiyar Science Award, conferred at Indian Science Congress – 2005.
- ❖ Acharya P.C. Ray Memorial at Indian Chemical Society convention at Marathwada University, Aurangabad on 24th December, 2006

Task Force Member/Research Council Member

- ➢ Examiner of Ph.D./M.Phil thesis: (1997):
  Delhi University,
  Osmania University,
  Lucknow University,
  Panjab University
  GND University, Amritsar.
  Bundelkhand University, Jhansi
  Kurukshetra University, Kurukshetra

- ➢ Chairman for "Eleventh Five Year Plan - Pharmaceutical, Health Care and Drug Sector under R&D Planning Division, Council of Scientific & Industrial Research, New Delhi.
- ➢ Expert member of FICCI for INDO-US join industry-working group on Biotechnology.
- ➢ Member for Selection Committee for NMITLI, CSIR, New Delhi
- ➢ Expert for evaluation of Council of Scientific & Industrial Research, Schemes - (1997 - present)
- ➢ Member – Executive Council, Bundelkhand University, Jhansi,Uttar Pradesh
- ➢ Member – Board of studies – Guru Gobind Singh Indrapastha

Ph.D. Guide

The following students have been awarded Ph.D. under my guidance/supervision:

1. Nawal Kishore, Ph.D. Chemistry
2. Ram Shankar Upadhayaya, Ph.D. Chemistry
3. Himadri Sen, Ph.D. Biological Science
4. Sharad Sharma, Ph.D. Biological Science
5. Rajan Goel, Ph.D. Biological Science
6. Jyoti Idnani, Ph.D. Pharmaceuticals

PATENTS:

1. Sudershan K. Arora, Neelima Sinha, Prathap Nair, Ajay Tilekar, Nabendu Saha, Talkha Khna, Reeba Vikramadithyan, and Rajesh Gupta (Lupin Limited) - Provisional Application filed for Indian Patent "Novel Anti-Diabetic Compounds".

2. Sudershan K. Arora, Neelima Sinha, Navnath Karche, Prasad Dixit, Karan Singh, Rajan Goel (Lupin Limited) - Provisional Application filed for Indian Patent "Novel Anti-Diabetic Compounds".

3. Sudershan K. Arora, et.al. Muscarinic Receptor Antagonists (Ranbaxy Lab. Ltd), International Application No. PCT/IB2005/003459, Dated 18th Nov. 2005 (RLL-625WO).

4. Sudershan K Arora et. al. (Lupin Limited) A Novel Anti-mycobacterial Pharmaceutical composition, US Patent Application # 10/844, 922 March, 2004.

5. Sudershan K. Arora et. el (Lupin Limited). A purified arabinogalactan-protein (AGP) composition useful in the treatment of psoriasis and other disorders" US Patent Application # US/10/931, 814 September, 2004.

6. Sudershan K. Arora et. el (Lupin Limited)., Herbal Composition for Treating various disorders including Psoriasis, filed a PCT application (US), application # US 10/340,195, January, 2003.

7. Sudershan K. arora et. al (Lupin Limited), A synergistic Aqueous Pharmaceutical Composition for Prophylactic Treatment of Migraine, filed a PCT application # PCT/IN03/00289 filed on August 27, 2003.

8. Sudershan K. Arora, Neelima Sinha, Rakesh Sinha (Lupin Ltd.) "Novel Antimycobacterial Compounds" filed a PCT application in August, 2002.

9. Sudershan K. Arora, V. K. Patil, Rakesh Sinha (Lupin Limited) "Novel 3-and/or 4-(4-substituted piperizinyl)alkyl pyrroles useful as Antitubercular Agents" filed a PCT application in August, 2002.

10. Sudershan K. Arora, V. K. Patil and Ajay Shankar (Lupin Ltd) " Novel Atibacterial Compounds" filed a PCT application in August, 2002.

11. Sudershan K. Arora, S. Narendar, Vandita Srivastava and D.B. Saraf (Lupin Limited) "Herbal Medication for the treatment of Psoriasis" filed in India on 8th day of January, 2002.

12. Anita Mehta, Sudershan K. Arora, et.al. (Ranbaxy Laboratories Ltd) "Novel Phenyl Oxazolidinone having antimicrobial properties" filed in India on July 17, 2000.

13. Ashwani Kumar Verma, Sudershan K. Arora, Jasbir Singh Arora, Ashok Rattan (Ranbaxy Laboratories Ltd) "Syntheses of New Azole Compounds As Therapeutic Agents for Fungal Infections" filed in USA on 23rd May, 2000.

14. Ashwani Kumar Verma, Sudershan K. Arora, Jasbir Singh Arora, Ashok Rattan (Ranbaxy Laboratories Ltd) "Process for the Syntheses of New Azole Compounds As Therapeutic Agents for Fungal Inections" filed in India on 7 th March, 2000.

15. Sudershan K. Arora, Nawal Kishore, Jang Bahadur Gupta, Vishwas D. Joshi: (Ranbaxy Laboratories Ltd) "Derivatives of Monosaccharides as Novel Cell Adhesion Inhibitors" filed in US on March 25, 1999; WO 00/42054.

16. Sudershan K. Arora; Nawal Kishore, Jang Bahadur Gupta, Vishwas D.Joshi : (Ranbaxy Laboratories Ltd) "A Process for the Synthesis of Derivatives of Monosaccharides as Novel Cell Adhesion Inhibitors" filed in India on January 15, 1999.

17. Sudershan K. Arora, Madan Pal Tanwar, Jang Bahadur Gupta, Geeta Sharma: (Ranbaxy Laboratories Ltd) "Derivatives of Monosaccharides as Novel Cell Adhesion Inhibitors" filed in US on January 12, 1999; WO 00/42053.

18. Sudershan K. Arora, Madan Pal Tanwar, Jang Bahadur Gupta, Geeta Sharma: (Ranbaxy Laboratories Ltd) "A Process for the Synthesis of Derivatives of Monosaccharides as Novel Cell Adhesion Inhibitors" filed in India on October 22, 1998.

19. Sudershan K. Arora et.al (Dexter Chemicals (1) Pvt. Limited): Disubstituted and trisubstituted derivatives of 2,3:4,6-DI-0-isopropylidene (x-L-Xylo-2-Hexulofuranosonic Acid having Anti-Cancer, Anti-inflammatory and Anti-Proliferative Activity (US Patent # 5, 637,570 June, 1997)

20. S.K. Arora (Medicarb Inc.): Derivatives of Pentoses Having Anti-Cancer, Anti-Inflammatory, and Anti-proliferative Activity. (U.S. Patent submitted January, 1993).

21. S.K. Arora (Medicarb Inc.): Disubstituted and Deoxy Disubstituted Derivatives of (x-D-Lyxofuranosides having Anti-Cancer, Anti-inflammatory and Anti -proliferative Activity: U.S. Patent # 5,360,793 (Nov. 1994).

22. S.K. Arora (Medicarb Inc.): Disubstituted and Deoxy Disubstituted Derivatives of a-D-Lyxofurabosides Having Anti-Cancer, Anti-inflammatory and Anti-proliferative Activity. (U.S.

Patent # 5,344,923 (Sept., 1994).

23. S.K. Arora, D. Thomson, Akhtar Nayeem: Anti -proliferative and Antiinflammatory Compounds: 5- or 6-D.eoxy hexose monosaccharides having a saturated nitrogen containing hetetrocycles at the 5- or 6-position: US Patent # 5,360,792 (Nov., 1994).

24. S.K. Arora, R.L. Whistler and A.V. Thomas: M6nosaccharides having AntiProliferation and Anti - Inflammatory Activity, composition and uses thereof. U.S. Patent# 5,298,494 (March, 1994).

25. S.K. Arora: Selective Hydrolysis of Diacetal blocked cyclic hexoses using 30% perchloric acid. (U.S. Patent submitted February 1990).

26. S.K. Arora and B, Ronsen: 3,5,6-Substituted Derivatives of 1,2-0-Isopropylidene- alpha, D-Glucofurnaose, and intermediates for preparing these derivatives. U.S. Patent # 5,010,058 April, 1991.

27. B. Ronsen, S.K. Arora and A.V. Thomas: Derivatives of alpha, DGlucofuranose and intermediates for preparing these derivatives. U.S. Patent # 4, 996, 195 February, 1991.

28. S.K. Arora, B. Ronsen: Solvent free synthesis of ethereally substituted blocked nonosaccharides and the selective hydrolysis thereof, U.S. Patent 5,344,924 (Sep., 1994).

29. J.A. Durden, T.D. Silva, S.K. Arora, CX Rao and R. Grover (Union 8Carbide Corporation, U.S.A.). N-(Alpha-haloacyl)-N-hydrocarbonyI carbomyl halides and process of preparation. U.S. Patent # 4,637, 901 (Jan. 20, 1987).

PUBLICATIONS:

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2. PP Dixit, VJ Patil, S Jain, RK Sinha, SK Arora, N Sinha. Synthesis of 1-[3-(4-benzotriazol-1/2-yl-3-fluoro-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-3-substitued-thiourea derivatives as antituberculosis agents. *European Journal of Medicinal Chemistry* 2006, 41, 423-428.

3. Biswajit Das, Sonali Rudra, Ajay Yadav, Abhijit Ray, S.K. Arora, et.al. Synthesis and SAR of novel oxazolidinones: Discovery of Ranbezolid, Bioorganic & Medicinal Chemistry Letters 2005, 15, 4261-4261.

4. Ahmed Kamal, K. Srinivasa Reddy, S. Kaleem Ahemd, M. Naseer, A. Khan, S.K. Arora, Anti-tubercular agents. Part 3. Benzothiadiazine as a novel scaffold for anti-Mycobacterium activity, Bioorganic & Medicinal Chemistry, 2006, 14, 650-658.

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6. PP Dixit, PS Nair, VJ Patil, S Jain, SK Arora, N Sinha. Synthesis and antibacterial activity of novel (un)substituted benzotriazolyl oxazolidinone derivatives. *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 3002–3005.

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8. A Kamal, AH Babu, AV Ramana, RK Sinha, JS Yadav, SK Arora. Antitubercular agents. Part 1: Synthesis of phthalimido- and naphthalimido-linked phenazines as new prototype antitubercular agents. *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 1923–1926.

9. N Sinha, S Jain, A Tilekar, RS Upadhayaya, N Kishore, GH Jana, SK Arora. Synthesis of isonicotinic acid *N'*-arylidene-*N*-[2-oxo-2-(4-aryl-piperazin-1-yl)-ethyl]-hydrazides as antituberculosis agents. *Bioorganic & Medicinal Chemistry Letters* **2005**, *15*, 1573–1576.

10. N Kishore, S Jain, N Sinha, RS Upadhayaya, R Chandra, SK Arora. Synthesis of some new disubstituted- and deoxytrisubstituted-α-D-allofuranoses. *ARKIVOC* **2005**, *(iii)*, 156–164.

11. N Sinha, S Jain, A Tilekar, RS Upadhayaya, N Kishore, RK Sinha, SK Arora. Synthesis and antimycobacterial activity of *N,N'*-disubstituted isonicotinohydrazide derivatives. *ARKIVOC* **2005**, *(ii)*, 9–19.

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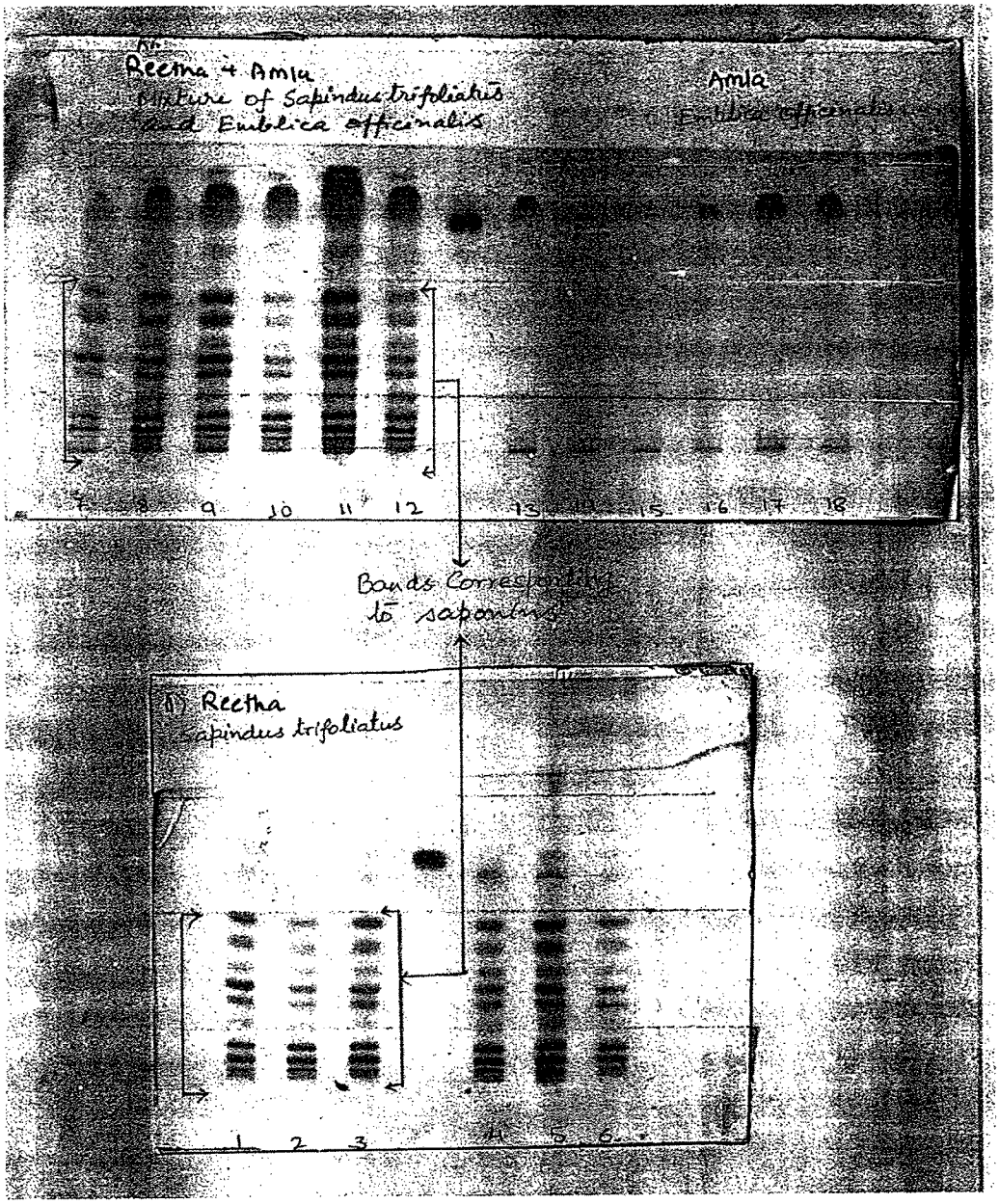
EXHIBIT 2

FIGURE : Comparison of Thin Layer Chromatographic (TLC) separation of the extracts and compositions of the present invention and Gupta et. al.:



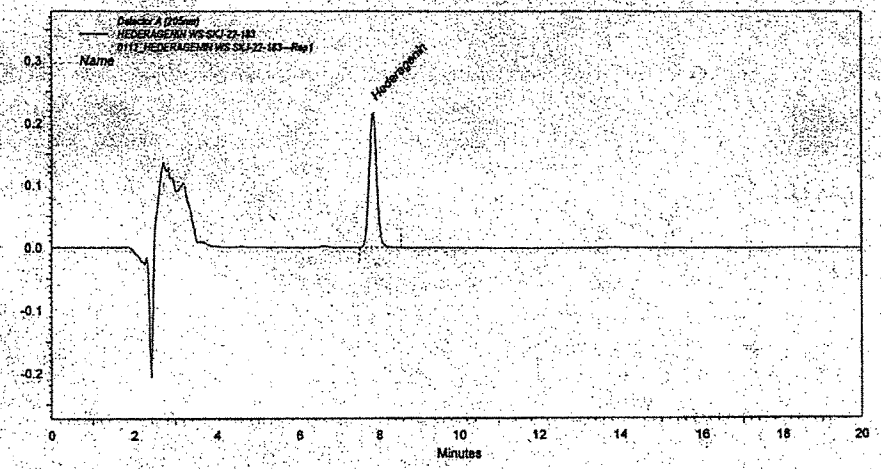
Spot no. 1: Raw material of present invention (*Sapindus trifoliatus)*
Spot no. 7: (1:1) Mix of *Sapindus trifoliatus* & *Emblica officinalis* (Raw material of Gupta et. al.)
Spot no. 13: Raw material of *Emblica officinalis* as reference
Spot no. 2: Composition of the present invention (1% w/v)
Spot no. 12: Composition of Gupta et al (1% w/v)
Spot no. 18: Composition comprising (1%w/v) of *Emblica officinalis* as reference

EXHIBIT 3

HPLC quantitative analysis of the compositions from Gupta et. al. and US 10/252,992 (*ref.: ANNEXURE-II*)

LUPIN LIMITED , PUNE (NCER)

Instrument No : NCER / PK / Inst-002 Reference No : LLL2011(78) Analyst : Hemant Sugandhi
Sample Name : ***HEDERAGENIN WS SKJ-22-183***
File Name : *E:\PUBLIC\JAN-2007\LLL2011\0112_HEDERAGENIN WS SKJ-22-183—Rep1*
Method Name : E:\PUBLIC\JAN-2007\LLL2011\ASSAY Method.met
Vial : *1* Inj. vol : *50 µL* Date Acquired : 1/13/2007 12:07:49 AM



Detector A (205nm)

Pk #	*Retention Time*	*Area Percent*	*Area*	Name
1	*7.85*	*100.00*	2844979	*Hederagenin*
Totals		*100.00*	2844979	

Figure - 1

Verified by

EXHIBIT 4

Assay report obtained from Novascreen, USA for Gupta et. al.

Gupta et al

Assay Report

NOVASCREEN

Client Name: Lupin Ltd. (Research Park)
Client Contact: Rajan Goel
Task Order Number: 06-3662

Barcode Number: 063662-1
Client Number: LLL6738
Solubility of Stock: Soluble

Receptor	Percent Inhibition (Average; N = 2) 2.5E0 ug/ml	2.5E2 ug/ml
NEUROTRANSMITTER RELATED		
GABA A, Agonist Site	19.21%	95.95%
Glutamate, AMPA Site (Ionotropic)	-0.89%	41.69%
Glutamate, Chloride Dependant Site (Ionotropic)	1.95%	84.35%
Glutamate, Kainate Site (Ionotropic)	-1.16%	25.68%
Glutamate, NMDA Agonist Site (Ionotropic)	15.26%	66.02%
Glutamate, NMDA, Glycine (Stry-insens Site) (Ionot	4.03%	42.60%
ION CHANNELS		
GABA, Chloride, TBOB Site	-14.60%	-3.77%
Sodium, Site 2	13.37%	3.30%

Values are expressed as the percent inhibition of specific binding and represent the average of replicate tubes at each of the concentrations tested. Bolded values represent inhibition of 50% or greater.

Assay report obtained from Novascreen, USA for Emblica officinalis alone

Assay Report

NOVASCREEN
a Caliper Life Sciences company

Client Name: Lupin Ltd.
Client Contact: Rajan Goel
Task Order Number: 06-3491

Barcode Number: 063491-1
Client Number: LLL-3064
Solubility of Stock: Soluble

Receptor	Percent Inhibition (Average; N = 2) 2.5E0 ug/ml	2.5E2 ug/ml
NEUROTRANSMITTER RELATED		
GABA A, Agonist Site	**64.09%**	**102.22%**
Glutamate, AMPA Site (Ionotropic)	**-10.07%**	**56.20%**
Glutamate, Chloride Dependent Site (Ionotropic)	28.28%	49.24%
Glutamate, Kainate Site (Ionotropic)	-1.12%	39.30%
Glutamate, NMDA Agonist Site (Ionotropic)	**14.92%**	**71.82%**
Glutamate,NMDA,Glycine (Stry-insens Site) (Ionot	0.48%	28.21%
ION CHANNELS		
GABA, Chloride, TBOB Site	-1.95%	-0.03%
Sodium, Site 2	7.11%	3.93%

Values are expressed as the percent inhibition of specific binding and represent the average of replicate tubes at each of the concentrations tested. Bolded values represent inhibition of 50% or greater.

EXHIBIT 5

NOVASCREEN, USA uses a criteria of 50% inhibition or greater to qualify a compound as active in binding experiments

NOVASCREEN

Interpreting your Data

Screening assays can provide valuable information about a compound's biological activity and selectivity. To understand and assess your data, NOVASCREEN suggests these guidelines for interpretation of the data presented:

Baseline, -20% to +20% inhibition:
In most assays, our standard baseline range runs from -20% to +20% inhibition of binding or enzyme activity. NOVASCREEN considers compounds showing results in this range inactive at this site.

Compounds which show negative inhibition(< 20%):
NOVASCREEN's assays are designed to test for inhibition of binding or enzyme activity. Occasionally, compounds, particularly naturally derived products and extracts, will demonstrate high negative inhibition (i.e., resulting from the extraction procedure used) and may, at the discretion of the client, warrant retesting at lower concentrations.

Compounds which show inhibition in the range of 20% to 49%:
Compounds exhibiting these results show marginal activity at the receptor site and generally do not warrant further examination unless otherwise directed by the client.

Compounds which show inhibition of 50% and greater:
NOVASCREEN uses a criteria of 50% inhibition (or greater) to qualify a compound as active. Active compounds tested at multiple concentrations can generally be expected to show a dose-dependent response and such follow-up studies are recommended at the client's discretion.